Trends in Vertebrate Pesticide Use and New Developments: New Zealand Initiatives and International Implications

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ABSTRACT: In New Zealand, sodium fluoroacetate (1080) has been used for vertebrate pest control for several decades. Since the 1990s, some 1080 users have switched to brodifacoum for possum and rodent control because of its ready availability and ease of use. An awareness that field use of brodifacoum results in persistent residues provides the impetus to develop alternatives and provide new tools and greater flexibility. Looking to the future, we seek toxins which increasingly combine "low-residue" characteristics with humaneness, and more selective bait and delivery systems enabling better and more acceptable control of possums, wallabies, mustelids, rodents, feral cats, and rabbits. Experience gained in the 1990s with the introduction of cholecalciferol (Feracol®) and a cyanide pellet (Feratox®), which both kill possums without secondary poisoning, underpins the extension in 2009 of the Feratox® registration to include introduced Dama wallabies. To date, zinc phosphide has not been registered in NZ, despite its field use in Australia and the U.S. and low secondary poisoning risk compared with 1080. Research and registration dossiers are being assessed in 2009-10 for zinc phosphide containing products for possum and rodent control. Registration documents are also being prepared for a combination of cholecalciferol and coumatetralyl to provide a slow-acting alternative to brodifacoum for the field control of possums, rodents, and rabbits with low risk of bio-accumulation. Anticipated timelines for product availability are 2010 (zinc phosphide) and 2011-13 (cholecalciferol and coumatetralyl). Our intention now is to move beyond these conventional rodenticides and develop new vertebrate pesticides. For example, we are pursuing the registration of *para*-aminopropiophenone (PAPP) for humane control of stoats and feral cats, and a series of related novel toxins and other compounds that target the red blood cell for other pest species including rodents. PAPP products should be available in 2010, subject to registration approvals. New research initiatives in 2010 will increasingly result in a shift in focus to the development of novel rodenticides aided by new international research collaborations.

KEY WORDS: 1080, cyanide, New Zealand, PAPP, *para*-aminopropiophenone, rodenticides, vertebrate pesticides

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INTRODUCTION

New Zealand wildlife evolved in the absence of mammalian predators (Parkes and Murphy 2003), and birds have been particularly affected by the introduction of non-native predators. Over 40% of the pre-human land bird species are now extinct in New Zealand, and the proportion of birds classed as threatened is one of the highest in the world (Clout 1997). Vertebrate pesticides such as sodium fluoroacetate (1080) are used to mitigate conservation problems and disease problems caused by

the impact of rodents and other introduced species, such as possums (*Trichosurus vulpecula*) (Seawright and Eason 1994). However, the use of 1080 and "the 1080 debate" in New Zealand has become more polarised since the Environmental Risk Management Authority (ERMA) reassessment in 2007 (Keating 2007, Hansford 2009, Philp 2009), and expenditure to meet increased compliance and consultation requirements continues to increase. Research on biocontrol of vertebrate pests has been an important and major focus for investment for more than 20 years in both New Zealand (NZ) and Australia (Hellstrom 2008). Despite considerable commitment, effort, and initiatives, there is a gap between conventional poisons and the requirements of modern biocontrol that needs to be filled (Tyndale-Biscoe and Hinds 2007, Hellstrom 2008). More alternatives to 1080 for the control of possums, mustelids, feral cats, rodents, and rabbits are required now to reduce over-reliance on 1080 and provide greater flexibility. With continued focused research effort, the next 1-6 years should see changes as improved, increasingly "eco-friendly" toxin products become available and additional products with novel active ingredients targeting possums and other major pests are delivered.

As a result of recent research and development:

i) Feratox® cyanide pellets are now being registered for wallaby control as well as possums,
ii) Registration documents are currently being assessed by the ERMA for zinc phosphide as an alternative to 1080 for the control of possums,
iii) New low-dose cholecalciferol baits have recently been proven to be effective for rodent and possum control,
iv) Registration documents are also being prepared for a combination of cholecalciferol and coumatetralyl to provide an anticoagulant alternative for effective possum control and further reduce the amount of cholecalciferol required, which is an expensive component, and
v) Anticipated timelines for product availability are 2010 (zinc phosphide and low-dose cholecalciferol) and 2011-13 (cholecalciferol and coumatetralyl) subject to ERMA and New Zealand Food Safety Authority (NZFSA) approvals and continued focused research and development effort.

Research and development is being achieved by our particular grouping of researchers and manufacturers. This ensures private sector commercialisation and product registration skills are linked in close collaboration with public sector and University expertise across a range of different science disciplines. In the following sections, we first describe the toxins commonly used in New Zealand for the control of unwanted mammals, and then we further review new research and development and product initiatives.

CURRENT VERTEBRATE PESTICIDES

Animal poisons, or 'Vertebrate Toxic Agents', fall into two classes: non-anticoagulant and anticoagulant agents. Those most commonly used in New Zealand are outlined below.

Non-Anticoagulant Compounds

Sodium fluoroacetate (1080) is effective for controlling pests in a variety of bait formulations and is the only poison commonly used for aerial control of pests in NZ. Carcasses of animals poisoned with 1080 are hazardous to dogs for many months (Meenken and Booth 1997), and there is some debate about the humaneness of 1080 (Sherley 2007, Littin et al. 2009).

Feratox® cyanide pellets were developed to increase the effectiveness of cyanide for possum control and reduce the risk of exposure for operators. Cyanide is potent, it does not cause secondary poisoning of dogs, it is favoured by some who oppose the use of 1080, and it is humane (Gregory et al. 1998). Whilst Feratox® cyanide pellets are very effective for possums and now wallabies, they have not yet been formulated for predator control.

Phosphorus is used by only a few licensed operators and is usually added to paste bait for possum control. It is generally considered inhumane (O'Connor et al. 2007), and its use has been associated with the secondary poisoning of dogs (Gumbrell and Bently 1995).

Cholecalciferol (vitamin D_3) was developed in NZ for controlling possums (Eason 1991) and is now registered in Feracol® paste bait, Pestoff DECAL Possum Bait®, and No Possum® gel, with Feracol® paste bait also now used for rodent control. There is low risk of secondary poisoning to dogs, and birds are much less susceptible to cholecalciferol than to 1080 (Eason et al. 2000), but current baits are deemed too expensive.

Anticoagulant Compounds

First-generation anticoagulant rodenticides were developed in the 1950s and 60s, and second-generation anticoagulants in the 1970s and 80s. Pindone has proved most effective for rabbit control. It is also registered for possum control but is not so effective in this species. Diphacinone is more toxic than pindone and is registered for field control of rodents. They do not bioaccumulate like the second-generation anticoagulants. Coumatetralyl is also registered for rodent control but is more persistent than diphacinone and pindone (Eason et al. 2008).

Brodifacoum is the most well known second-generation anticoagulant and has been used successfully in recent rodent eradication programmes on offshore islands to protect populations of endangered indigenous birds. Although brodifacoum is effective for possum and rodent control, repeat field use of brodifacoum can result in transfer of residues through the food chain (Eason and Spurr 1995, Dowding et al. 1999, Eason et al. 1999).

REGISTRATION PROCESSES AND TRENDS

In NZ, the requirements of the Hazardous Substances and New Organism Act (1996) legislation must be met, along with the requirements of the Agricultural Chemistry and Veterinary Medicines Act (1997). The registration process requires approval from both the Environmental Risk Management Authority (ERMA) and the New Zealand Food Safety Authority (NZFSA). Consultation with Maori, the indigenous people of New Zealand, is a prerequisite, and welfare considerations are a key component of the registration assessment process

for vertebrate pesticides, as well as the need for demonstrating effective control of pests with minimum non-target impacts.

THE PIPELINE

New NZ Registration of Established Vertebrate Pesticides

Part 1: Products that Contain Vertebrate Pesticides Already In Use in NZ

The use and registration of existing products and active ingredients that are already approved by ERMA and the NZFSA and viewed as "eco-friendly" are being extended. Since its registration in 1997, Feratox® has become an accepted method for cyanide baiting with more than 6 million pellets sold annually for possum control. As its use has strong community support and it is used by hunters and trappers as well as professionals, extending this registration to include the Dama wallaby (*Macropus eugenii*) and Bennetts wallaby (*M. rufogriseus*) is a logical step (Eason et al. 2010d, Shapiro et al. 2010a).

Cholecalciferol has the advantage of low secondary poisoning risk and low toxicity to birds (Eason et al. 2000, Eason et al. 2010a). Currently available commercial baits contain cholecalciferol at a concentration of 0.8%. The active ingredient cholecalciferol is expensive, and if efficacy and humaneness can be achieved with lower concentrations of toxin in existing baits, their price could be reduced. Field trials are planned in both paste and solid baits in 2009 to support product registration of affordable effective bait containing 0.4% cholecalciferol.

Cholecalciferol + coumatetralyl (C+C) as a combination also has a track record overseas; e.g., Racumin Plus® has been used to overcome anticoagulant resistance in rats and mice (Pospichil and Schnorbach 1994). The New Zealand Animal Health Board has funded the development of 'C+C' for controlling possums, and recently this was further developed in multispecies baits for controlling rats and mice as part of the Lincoln University Foundation for Research, Science and Technology (FRST) programme that was completed in 2009. Bait containing 0.015% cholecalciferol and 0.03% coumatetralyl (C+C) has been developed, and dossiers are being prepared for registration later in 2009. C+C is effective at killing possums, rodents, and rabbits even though the amount of cholecalciferol is a fraction of that used in current products.

Part 2: Products that Contain Vertebrate Pesticides Not Already In Use in NZ

Zinc phosphide has been in use for over 50 years with very few non-target hazards. It is still used in the U.S. as well as in Australia, China, and the Asia-Pacific region for field control of rodents and larger pests. It found favour because of the comparatively low risk of secondary poisoning of dogs compared with 1080 (Hood 1972, USEPA 1998). Zinc phosphide is a quick-acting compound with clinical signs first appearing from 15 minutes to 4 hours, and death after a lethal dose occurs in possums and rodents generally in 3-12 hours (Ross and Henderson 2006). It is inexpensive and it has not been registered in NZ before now (Table 1).

Whilst zinc phosphide is more akin to 1080, in that it kills more quickly than anticoagulants, C+C by contrast is slower acting and offers the advantages of brodifacoum without persistent residues. For both zinc phosphide and C+C, there is a common development strategy, which is to first register a product for control of possums and then extend this registration to include rodents and rabbits. Zinc phosphide is initially being registered in a paste bait. Ultimately, it is intended that there will be solid bait and paste formulations of both zinc phosphide and C+C (Ray Henderson, PestTech NZ, pers. comm.).

Table 1. A forecast for the new registration pipeline goals for the NZ commercial partners in new product developments described in this paper, subject to ERMA / NZFSA and continued focused research effort.

Type	2010	2011	2012	2013	2014	2015
Products that contain vertebrate pesticides already in use in NZ.	Feratox® for Bennett's wallaby control Low-dose (0.4%) cholecalciferol paste and solid bait	Diphacinone solid bait	C+C solid bait for multispecies control	C+C paste bait for multispecies control of possum, rats, mice and rabbits	D+C paste bait for multispecies control of possum, rats, mice and rabbits	
Products that contain vertebrate pesticides NOT already in use in NZ.	Zinc phosphide 1.5% paste for possum	Zinc phosphide 1.5% paste for possums rodents		Zinc phosphide solid baits for possums and rodents		
NZ registrations of a new generation of vertebrate pesticides	PAPP paste for stoat and feral cat control	PAPP for cats and ferrets PAPP delivered in repeat dose tunnels for stoats	Sodium nitrite for nuisance feral pigs PAPP delivered in repeat dose tunnels for cats	Sodium nitrite for possums Multi-species tunnels	More potent PAPP like rodenticide and/or combined rodenticide and mustelid toxin Possum tunnels	PAPP like possum selective toxin + other RBC toxins Natural toxins. Tunnels with sensors

Part 3: NZ Registrations of a New Generation of Vertebrate Pesticides

Internationally, there have been no new toxin developments resulting in new product registrations for mammalian pest control since the development of brodifacoum and cholecalciferol in the 1970/80s. There have been a number of initiatives to produce specific rodenticides (Roszkowski et al. 1964) and revitalization of these could result in toxins that target *Rattus norvegicus* (Nadian and Lindblom 2002, Brimble et al. 2004, Steel et al. 2004). There remains an opportunity, and a challenge, to go beyond the registration of current rodenticides, and also to target mice and other species of rats with one toxin. A new class of compounds is now emerging, and we are developing these toxins as rodenticides (Table 1). At the core of the research is the discovery that targeting red blood cells (RBCs) induces a humane death. PAPP (*para*-aminopropiophenone) represents the first compound in this class and is a potent and selective toxin for stoat and feral cat control (Murphy et al. 2007, Eason et al. 2010c). In research being initiated by Lincoln University with Connovation Ltd. and associates, we seek a quantum leap forward with the development of new class of replacements that target RBCs and are ahead in terms of humaneness and safety.

Desirable features for emerging rodenticide toxins can be broadly characterised under the headings of efficacy, environmental consideration, and suitability for commercialisation: i) lethal to rats and mice, ii) relatively humane vs. other rodenticides (most are inhumane), iii) orally active and rapidly absorbed, iv) relatively short half-life in blood/organs vs. other rodenticides (many have long half-lives), v) not persistent in the environment, vi) do not lead to secondary poisoning, vii) have an antidote, viii) reasonable shelf life, and ix) reasonable cost.

The first products to emerge will not be rodenticides but will be PAPP-based baits, and then these will be coupled with unattended delivery devices that will facilitate control of mustelids for lengthy periods. A tunnel system designed with compressed CO_2 gas will propel a measured amount of PAPP paste onto the abdomen of pests as they pass over a trigger. A dose is delivered orally when the animal licks and grooms its abdomen. Cage trials have achieved the proof-of-concept stage for this method of killing stoats, indicating that a device capable of safely delivering multiple lethal doses of toxin without regular resetting can be produced (Hix et al. 2009a,b), which should enable larger areas of land to be treated.

Recent progress, following field trials in 2008 (stoats), and 2008 and 2009 (cats), has been rapid. PAPP dossiers for chemistry and manufacturing, toxicology, efficacy, ecotoxicology, non-target impacts, and welfare were filed with the NZFSA in 2008 and ERMA in 2009. In field trials in 2008, PAPP has already been shown to be effective at killing stoats (Shapiro et al. 2010b), indicating that it has considerable potential for threatened bird protection programs, such as for kiwi (*Apteryx* spp.) and kaka (*Nestor meridionalis*). Amongst this class of compounds, PAPP represents a partially selective toxin. PAPP is toxic to carnivores, with birds and humans being less sensitive (Eason et al. 2010b). The onset of symptoms is rapid, and stoats and feral cats are usually unconscious quickly. Methylene blue is an effective antidote to PAPP toxicity and is available from veterinarians.

Sodium nitrite is a common salt that is currently at an early stage of research and investigation for larger pests. It is being developed in Australia for the control of feral pigs (Cowled et al. 2008), and in New Zealand cage trials have recently been completed indicating that it may have potential for controlling possums. The toxicology of sodium nitrite is well understood because of its use as a preservative agent in meat. The toxic effects of sodium nitrite, like PAPP, are related to its ability to reduce the oxygen carrying capacity of the red blood cell, and methylene blue is also an antidote for it.

On the platform of PAPP and sodium nitrite, alternative red blood cell (RBC) toxicants are being explored for rodents. These "RBC toxins" must be safer toxins, designed to minimise the impact of invasive animals, exhibiting humane performance, and having a simple antidote. For example, synthesis and screening of PAPP analogues that also target red blood cells has been initiated, and these are being tested *in vitro* as well as in animals. PAPP and sodium nitrite should be perceived as the prototypes, and we believe that we can improve on these compounds to produce more potent, broad spectrum, and selective species specific toxins with low toxicity to birds, for a range of pest species, based on the PAPP platform, which will facilitate more effective predator and rodent control.

Other initiatives include Maori-led research to identify useful natural plant toxins. Whilst this avenue of research may appear a long shot, a component of the native plant karaka (*Corynocarpus laevigatus*), like PAPP, induces methaemaglobinaemia and has already been proven to be toxic to possums (Gregory et al. 2000).

CONCLUSIONS

Over the last three decades, considerable effort has been put into improving and refining the use of 1080 in New Zealand. By contrast, the last twelve months has seen a record period for new product registration advancement. Extensive registration dossiers were filed with ERMA and NZFSA for microencapsulated zinc phosphide (MZP) for possums, Feratox® for wallabies, and *para*-aminopropiophenone (PAPP) for stoats. However, there are no "silver bullet" replacements for 1080 (Hansford 2009). A suite of more effective and acceptable tools and advanced delivery systems is being developed in order to reduce over-reliance on 1080 and to provide greater flexibility. There is now an intense focus on delivery of alternatives within 1-6 years. A new consortium, linked with Lincoln University, is working to a timeline to deliver a suite of improved ecofriendly toxin products, as well as products with novel red blood cell toxins targeting rodents, possums, and other major pests, by 2015 (Table 1). Past research has focused on refining the use of 1080 (Seawright and Eason 1994). We are now moving into replacement mode, and if we can achieve the registration of PAPP, it will be the first new vertebrate pesticide for mammalian pest control in 30 years.

The new RBC toxins will be unique, exhibiting humane performance, availability of an antidote, improved efficacy, cultural acceptability, and species selectivity, and will fill a gap between conventional poisons and the demands and expectations of modern biocontrol. Development of these safer toxins may also help to increase direct involvement by communities in pest control initiatives. The improved safety to humans means that these toxins may be more accessible than current alternatives, such as 1080, which can only be used by licensed operators. These toxins also lack the downside of bioaccumulation, which the easily accessible anticoagulant toxins possess. The ability of volunteer-based community programs to become more involved in pest control will hopefully lead to greater community participation and better understanding of conservation issues.

Questions to be addressed in future research include:

i) What are the precise modes of action of natural toxins and other poisons that interfere with the O_2 carrying capacity of red blood cells and can a more systematic approach be taken to their discovery and development?

ii) What are the pathophysiological mechanisms underlying species variation in responses to these agents?

iii) In what ways are species specific food preferences linked to taste, texture, shape and olfactory and visual cues?

iv) Can reliable delivery systems be produced to effectively deliver toxins for lengthy periods without regular resetting?

Whilst this paper has a focus on product development in New Zealand, the development of PAPP and sodium nitrite has been advanced with colleagues in the Invasive Animals CRC in Australia. It builds on initiatives at the National Wildlife Research Center in the U.S. (Savarie et al. 1983), toxicology research in the UK on methaemoglobinaemia inducers (Marrs et al. 1991), and research in Australia (Marks, 2001, Marks et al. 2004, Cowled et al. 2008). There is growing interest in the development of novel rodenticides in the U.S. and in Europe, and further international collaboration is anticipated in 2010 and beyond to help accelerate the development of new rodenticides.

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